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10/680,402	10/07/2003	John N. Feder	D0045A CIP	7514

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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	**Application No.** 10/680,402	**Applicant(s)** FEDER ET AL.
	Examiner Jon M. Lockard	**Art Unit** 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-38* is/are pending in the application.

4a) Of the above claim(s) *30 and 32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31 and 35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group V, claims 15-16 and 18, drawn to a method of diagnosing a pathological or a susceptibility to a pathological condition by determining the presence or amount of a polypeptide, in the reply filed on 13 October 2005 is acknowledged. Applicant's further election of Alzheimer's disease as the disorder or condition in the reply filed 13 October 205 is acknowledged.

2. Newly submitted claims 30 and 32-34 are directed to an invention that is independent or distinct from the elected invention of Group V for the following reasons: claims 30 and 32-34 are directed to a method of diagnosing a pathological or a susceptibility to a pathological condition by determining the presence or amount of a nucleic acid.

3. The methods of claims 30 and 32-34 and the elected invention of Group V are drawn to patentably distinct methods. Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P § 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: they utilize different starting materials and methods steps and require non-coextensive searches.

4. Therefore, a search and examination of all the methods of claims 30 and 32-34 and the claims of the elected invention of Group V in one patent application would result in an undue burden, since the searches for the Inventions' methods are not co-extensive.

5. Accordingly, claims 30 and 32-34 as they are drawn to methods of diagnosing a pathological or a susceptibility to a pathological condition by determining the presence or

amount of a nucleic acid are withdrawn from further consideration as being non-elected by original presentation.

6. The restriction requirement is still deemed proper and is therefore made **FINAL**.

Status of Application, Amendments, and/or Claims

7. The preliminary amendment filed 07 September 2004 has been entered in full. Claims 1-28 are cancelled and claims 29-38 have been added. Claims 29-38 are currently pending, and claims 30 and 32-34 have been withdrawn from further consideration as discussed above. Therefore, claims 29, 31, and 35-38 are the subject of this Office Action.

Information Disclosure Statement

8. The information disclosure statement filed 24 October 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. A copy of the Incyte clone ID:6274179 reference has not been provided.

Specification

9. The disclosure is objected to because of the following informalities:

10. The disclosure is objected to because it contains numerous embedded hyperlinks and/or other form of browser-executable code. See for example, page 71, lines 27-28 and page 98, line

28. Applicant is required to delete the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

11. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is suggested.

Claim Rejections - 35 USC § 112, First Paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 29, 31, and 35-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

14. The claims are drawn to a method of diagnosing Alzheimer's disease comprising determining the expression level of a polypeptide of SEQ ID NO:2 or a fragment thereof in a normal brain sample and a brain test sample, wherein an elevated expression level of said polypeptide in said test sample relative to the expression level of said polypeptide in said normal sample is indicative of Alzheimer's disease or a predisposition to Alzheimer's disease.

15. The specification teaches that the results from quantitative PCR demonstrate that the mRNA encoding the HGPRBMY9 protein of SEQ ID NO:2 is overexpressed in human hippocampus tissue isolated from Alzheimer's patients as compared to normal human

hippocampus tissue (See pg 20, lines 7-15, Figure 14). However, even though the data have clearly demonstrated overexpression of the mRNA encoding the HGPRBMY9 protein of SEQ ID NO:2 is overexpressed in human hippocampus tissue isolated from Alzheimer's patients, such would not be predictive of overexpresion of the HGPRBMY9 protein encoded thereby. The data presented in the specification do not demonstrate that the encoded protein was overexpressed, such that it could be used as a diagnostic target for Alzheimer's disease. More importantly, the art teaches that it does not necessarily follow that an increase in DNA or mRNA copy number results in increased polypeptide expression, such that the HGPRBMY9 polypeptide of SEQ ID NO:2 would be useful as a diagnostic target for Alzheimer's disease. For example, as discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). Similarly, Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) disclose that only twenty-eight of the 165 protein blots they examined (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found (r= -0.025), if the average levels of mRNA or protein among all samples were applied across the 165 protein blots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance. Therefore, data pertaining to

HGPRBMY9 nucleic acids do not necessarily indicate anything significant regarding the HGPRBMY9 polypeptides. Thus, there is no guidance in the specification to enable one of ordinary skill in the art to determine, without undue experimentation, whether or not the HGPRBMY9 polypeptide is overexpressed in Alzheimer's disease to the extent that it could be used as a diagnostic, and the art indicates that it is not the norm that gene amplification, or even increased transcription, results in increased protein levels.

16. Thus, the identification that the HGPRBMY9 mRNA is overexpressed in Alzheimer's disease would not be accepted by those of skill in the art as being predictive of the expression levels of the HGPRBMY9 polypeptide, and it would require undue experimentation to determine such.

17. Furthermore, even if increased mRNA levels were predictive of an increase in proteins levels, claims 29, 31, and 35-38 would remain rejected under 35 U.S.C. § 112, first paragraph.

18. While the specification teaches that the mRNA encoding the HGPRBMY9 protein of SEQ ID NO:2 is overexpressed in human hippocampus tissue isolated from Alzheimer's patients as compared to normal human hippocampus tissue (See pg 20, lines 7-15, Figure 14), it does not teach differential expression in other brain regions which are encompassed by the claims. As the specification does not teach other brain regions which demonstrate a differential expression of the mRNA encoding the HGPRBMY9 protein of SEQ ID NO:2, undue experimentation would be required of the skilled artisan to determine such.

19. Additionally, the Specification teaches that the results from quantitative PCR demonstrate that the mRNA encoding the HGPRBMY9 protein of SEQ ID NO:2 is overexpressed in human hippocampus tissue isolated from Alzheimer's patients. However, the

specification does not teach a commensurate number of fragments which, based on the language of the claims, reads on a fragment of SEQ ID NO:2 consisting of as few as 2 amino acids, nor does it teach polypeptide variants that comprise at least 7 contiguous amino acids of SEQ ID NO:2 that are useful as peptide specific probes of SEQ ID NO:2. The specification also does not teach functional or structural characteristics of the amino acid variants and fragments of SEQ ID NO:2, as well as completely unrelated polypeptides which are encompassed the claims. Based on the limited number of disclosed species, it is not at all predictable that the claimed variants would be specific for the polypeptide of SEQ ID NO:2 or that they would be diagnostic of Alzheimer's disease, and it would require undue experimentation to determine such. As the specification does not teach how to make and use a number of species that would be commensurate in scope with the claims, it would require undue experimentation by the skilled artisan to practice the invention in a manner commensurate in scope with the claims, given the lack of guidance in the specification and the very broad scope of the claims.

20. Furthermore, while the Specification teaches several assay protocols for measuring the HGPRBMY9 protein of SEQ ID NO:2 (See pg 52, lines 5-14; pg 82, lines 5-16), it does teach how to use the claimed methods in a manner that would not produce brain damage to the individual from which the test sample was taken. While it is routine in the art to look at gene or protein expression in post-mortem brain tissue samples, the Examiner is not aware of any instance in the art in which brain samples, in particular samples of human hippocampus, are obtained from a living, healthy or diseased, patient for the purpose of diagnosing a disease/disorder or determining a predisposition to a disease/disorder. There are no methods or working examples disclosed in the instant application whereby a brain tissue sample is obtained

from a living healthy individual or a living diseased individual, and it would require undue experimentation of the skilled artisan to determine how to do so. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation since the specification has not taught how to practice the claimed invention without causing undue harm to the individual from which the brain tissue sample is obtained.

21. Due to the large quantity of experimentation necessary to determine whether or not the HGPRBMY9 protein of SEQ ID NO:2 is overexpressed in human hippocampus tissue isolated from Alzheimer's patients as compared to normal human hippocampus tissue; the lack of direction/guidance directed to the same; and the absence of working examples directed to same; the lack of direction/guidance presented in the specification regarding how to obtain a brain sample without causing undue harm to the individual from which the brain tissue sample is obtained; the absence of working examples directed to same; and the breadth of the claims which fail to recite any structural or functional limitations of HGPRBMY9 variants and which regions of the brain the samples may be obtained from; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

22. Claims 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

23. The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see 37 C.F.R.§1.808(a)). Examiner acknowledges the deposit of organisms under accession number PTA-2675 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, in order to be fully compliant with the requirement, applicants must state that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 C.F.R.§1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

24. In addition the identifying information set forth in 37 C.F.R.§1.809(d) should be added to the specification. See 37 C.F.R.§§ 1.803-1.809 for additional explanation of these requirements.

Summary

25. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback,** can be reached on **(571) 272-0961**.

The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JML
December 22, 2005

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER